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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	09/972,245	ROBERTS ET AL.
	Examiner	Art Unit
	Richard Schnizer, Ph. D.	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 09 May 2008.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 and 41-46 is/are pending in the application.

4a) Of the above claim(s) 14-16 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-13, 17-22 and 41-46 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The previous indication of allowance of claims 1-22 and 41-46 is hereby withdrawn. Claims 1-13, 17-22 and 41-46 are anticipated or rendered obvious by the prior art for the reasons set forth below. As a result linking claims 1-6 and 17-19 are not allowable, and claims 14-16 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/10/03.

An amendment under 37 CFR 1.312 was entered on 5/9/08, and claims 23-40 were canceled.

Claims 1-22 and 41-46 are pending, claims 14-16 are withdrawn from consideration, and claims 1-13, 17-22 and 41-46 are under consideration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 7, 9, 10, 17-19, 41-46 are rejected under 35 USC 102(b) as being anticipated by Wang et al (Canc. Res. 53:4588-4594, 1993).

Wang studied the antitumor activities of differentially PEGylated immunotoxins at several time points after multiple administrations of each differentially PEGylated immunotoxin.

TGFαR[29]-L2-C_H2-PE38QQΔ (TCP) is a recombinant immunotoxin composed of transforming growth factor a (TGFα) fused to a 38 kDa fragment of Pseudomonas exotoxin. Human IgG4 constant region C_H2 and a tetradecapeptide linker, L2, are inserted between TGFα and PE38. L2 and C_H2 have a combined 13 lysine residues as potential PEG-modification sites. mPEG conjugates of TCP (PEG-TCP) were generated, and the antitumor activity of two differentially modified species, B4 and B6, was studied.

Mice were inoculated with A431 tumor cells on day 0, and the modified B4 and B6 were administered to tumor bearing mice on days 4, 5, and 6. Tumor volume was measured at day 4 and every other day thereafter through day 12. See Fig. 6 on page 4591. So, Wang taught a method in which the two TCPs PEGylated to different extents were administered to different mice on day four, and the antitumor activity of the LMB--2s was measured at days 6, 8, 10,and 12. More of each PEG-TCP was administered on day 5, and the antitumor activity was measured at days 6, 8, 10, and 12. More of each PEG-TCP was administered on day 6, and the antitumor activity was measured at days 8, 10, and 12. Thus Wang taught all of the method steps of the claims, and so anticipates the claims.

Regarding claims 18 and 19, the PEGylated immunotoxins were delivered in PBS. Absent evidence to the contrary, the buffering of PBS protects the therapeutic agent.

Claims 1, 5-7, 9, 10, 17-19, 41-46 are rejected under 35 USC 102(a) as being anticipated by Tsutsumi et al (PNAS 97(15): 8548-8553, 2000).

Tsutsumi taught a method in which the antitumor activities of differentially PEGylated immunotoxins was measured at several time points after multiple administrations of each differentially PEGylated immunotoxin.

Anti-Tac(Fv)-P38 (LMB-2) is a recombinant immunotoxin composed of a 38 kDa fragment of Pseudomonas exotoxin fused to a single-chain Fv fragment of the anti-human Tac monoclonal antibody to the IL-2 receptor alpha subunit. The antibody portion of the fusion protein serves to target the exotoxin to tumor cells that display the IL-2 alpha subunit as a marker.

LMB2 has produced major clinical responses in hematologic malignancies, but exhibits toxic side effects caused by non-specific binding to non-target cells. It s also possible that specific binding to non-tumor cells that express the IL-2 receptor alpha subunit occurred. Also, patients developed an immune response to LMB-2 that reduces its therapeutic usefulness.

Tsutsumi, sought to increase the serum half-life, stability, and potency of LMB-2 by PEGylation. A single cysteine residue was engineered into the peptide connector that links the Fv region to the toxin. This cysteine residue was modified by attachment

of either 5 or 20 kDa PEG-maleimide. Mice were inoculated with ATac-4 solid tumor cells on day 0, and the modified LMB-2s were administered to tumor bearing mice on days 4, 6, and 8. Tumor volume was measured at day 4 and every other day thereafter through day 20. See Fig. 4 on page 8551. So, Tsutsumi taught a method in which the two LMB-2s PEGylated to different extents were administered to different mice on day four, and the antitumor activity of the LMB-2s was measured at days 6, 8, 10, 12, 14, 16, and 20. More of each LMB-2 was administered on day 6, and the antitumor activity was measured at days 8, 10, 12, 14, 16, and 20. More of each LMB-2 was administered on day 8, and the antitumor activity was measured at days 10, 12, 14, 16, 18, and 20. Thus Tsutsumi taught all of the method steps of the claims, and so anticipates the claims.

Regarding claims 18 and 19, the PEGylated immunotoxins were delivered in PBS. Absent evidence to the contrary, the buffering of PBS protects the therapeutic agent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5- 7, 9, 10, 12, 13, 17, 18, 41-46 are rejected under 35 USC 103(a) as being unpatentable over the combination of Kawashima et al (Leukemia Res. 15(6):

525-530, 1991), Ettinger et al (Cancer 75: 1176-1181, 1995), Saito et al (Leukemia (1997 Apr) Vol. 11 Suppl 3, pp. 408-9), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Kawashima reported on the treatment patients with hematological malignancies with 2, 4 - bis(*o*-methoxypolyethylene glycol)-6-chloro-S-triazine-conjugated L-asparaginase (PEG_2-ASP). One patient, suffering non-Hodgkin's lymphoma, received treatment with unmodified L-asparaginase and suffered severe nausea, vomiting and loss of appetite. The patient went into remission, but later relapsed and was then treated with weekly or twice weekly intravenous infusion of PEG_2-ASP, leading to complete remission within 2 months. The patient remained in complete remission for over one year with weekly infusions of PEG_2-ASP. During this period blood asparagine was assayed but was not detectable. Assays performed throughout the course of treatment included asparaginase activity determinations, and measures of erythrocytes, lymphoid cells, granulocytes, and blast cells. See Fig. 1 on page 527 and Figs 2 and 3 on page 528. The levels of these cells are considered to be indirect measures of asparaginase activity. So, Kawashima taught a method of determining activities of PEG_2-ASP in vivo after, and between, multiple administrations of the drug.

Ettinger reported the results of a multi-center study of monomethoxypolyethylene glycol succinimidyl)74-L-asparaginase (Oncaspar or PEG-L-asparaginase). Patients suffering from acute lymphoblastic leukemia, who had previously been treated with unmodified L-asparaginase, received PEG-L-asparaginase at days 1 and 14 of treatment. Evaluations of complete blood count, differential and platelet count were

performed prior to treatment, and were repeated on days 14 and 28 and before each administration of PEG-L-asparaginase thereafter. Bone marrow aspiration, and peripheral blood count were performed on day 0, day 14, and day 35. Patients were assessed for response by measurement of leukemic blasts, hypocellularity of bone marrow, and peripheral blood counts. Two thirds of evaluable patients achieved complete remission. See Fig. 1 on page 1177, and page 177, column 2, under "Clinical Laboratory Evaluation", and "Response Criteria". See also page 1178, column 1, last two paragraphs. The levels of these cells are considered to be indirect measures of asparaginase activity. So, Ettinger taught a method of determining activity of PEG-L-asparaginase in vivo after and between multiple administrations of the drug.

Saito studied the antitumor activity of L-asparaginase modified with a comb-shaped copolymer of polyethylene glycol and maleic anhydride (PM-asparaginase). Mice were inoculated intraperitoneally with murine lymphoma cells, and then received unmodified L-asparaginase or PM-asparaginase. Five out of six mice treated with PM-asparaginase were alive at day 60 and were free of tumors. PM-asparaginase had increased antitumor activity relative to unmodified asparaginase. See paragraph bridging pages 408 and 409.

Francis taught that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be affected by the way in which the protein drug is PEGylated. See abstract, and pages 2-4. Francis also taught that PEGylation of protein drugs can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Important considerations include the site of attachment of

PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis taught that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a PEGylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

So, the prior art taught that the type and extent of PEGylation of therapeutic proteins could affect their activity and immunogenicity, such that it would be obvious to optimize these variables (see Francis above), and that PEGylation can also affect the bioavailability of the protein (see Ettinger at e.g. page 1176, column 2, second full paragraph of introduction). The cited prior art also taught three different forms of L-asparaginase, each modified differently with a polyethylene glycol or a polyethylene glycol derivative. Given that all three forms of L-asparaginase had anticancer activity, it would have been obvious to one of ordinary skill in the art at the time of the invention to compare the efficacies of each of the different L-asparaginase forms in order to see which performed best in treating a given disease. In so doing it would have been obvious to follow the protocol of Kawashima in which the activity of L-asparaginase in blood was determined throughout the course of treatment, and in which blood counts, including blast cells, were performed throughout treatment. It would have been similarly obvious to use the protocol of Ettinger in which the effects of L-asparaginase on blast

cells and peripheral blood cells were measured. In other words, it would have been obvious to perform the routine assays that are generally done to determine the effect of L-asparaginase on disease progress throughout the course of treatment. It would also have been obvious to measure the actual catalytic activity of the enzyme throughout the course of treatment, as taught by Kawashima. The presence of that catalytic activity is what provides a therapeutic effect, so one would clearly have been motivated to determine its presence over the course of treatment. Further, the assays of blood components are considered to be indirect measurements of L-asparaginase activity. One would have been motivated to perform such studies to determine which modified version of L-asparaginase performed the best, particularly in view of the teachings of Saito, who indicated that differentially modified asparaginases had different performance characteristics, i.e. Saito taught that PM-asparaginase reduced immunoreactivities at lower degrees of modification than PEG_2-asparaginase. See Introduction on page 408. One of ordinary skill also appreciates that different modifications may lead to differences in enzyme activity, immunoreactivity, and circulation time (see Francis and Ettinger, above). Accordingly, it would have been obvious to perform comparisons of activity in vivo.

Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the optimization process suggested by Francis, and different chemistries result in different

modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph. Accordingly, it would be obvious to determine the relative catalytic activity of differently modified versions of L-asparaginase over the course of treatment, because there was reason to believe that some versions might be more or less active than others, and because it was routine in the art to make such measurements, as evidenced by Kawashima.

Claim 4 is obvious in view of the Kawashima, Ettinger, Saito, and Francis applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, 18, and 41-46 above, and further in view of Petersen et al (US 6,531,122, of record).

The teachings of Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also taught that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references do not teach SBA-, SC-, and ALD-PEGs.

Petersen taught that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25;

column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, it was apparent from the teachings of Francis that bioactivity, stability, immunogenicity, and toxicity of a protein drug may be differentially affected by the way in which the protein drug is PEGylated. See abstract. Thus it would have been obvious to use different linkages in the process of optimizing these result-effective variables.

Thus the invention as a whole was prima facie obvious.

Claim 8, 11, and 20-22 are obvious in view of the Kawashima, Ettinger, Saito, and Francis applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, 18, and 41-46 above, and further in view of Abuchowski et al (Cancer Treat Rep 63(6): 1127-1132, 1979).

The teachings of Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from Pseudomonas.

Abuchowski taught treatment of tumors in mice by administration of Achromobacter glutaminase asparaginase rendered nonimmunogenic by modification with polyethylene glycol. The resulting enzyme had greatly enhanced half life in blood and increased the survival of experimental mice inoculated with tumor cells when compared with unmodified glutaminase asparaginase. Abuchowski measured asparaginase activity in blood over time after a single injection of enzyme, and also measured mouse weight throughout the course of treatment in which mice were given PEGylated enzyme on alternate days. See Figures 3 and 4 on pages 1130 and 1131.

It would have been obvious to one of ordinary skill in the art at the time of the invention to further study and compare differently modified Achromobacter glutaminase asparaginases in the process of optimizing PEGylation of this enzyme. One would have been motivated to do so because it was clear to those of ordinary skill in the art at the time of the invention that the amount and type of PEGylation was a result effective variable that influenced the activity of the enzyme as well as its serum half life and immunogenicity, as taught by Francis. In doing so it would have been obvious to determine the activity of the differently modified drugs by assay of catalytic activity as taught by Kawashima and Abuchowski. It was routine in the art at the time of the invention to follow the progress of a disease over the course of treatment (as evidenced by Kawashima and Ettinger), thereby obtaining an indirect measure of drug activity. It was similarly routine to directly measure the catalytic activity of an enzyme drug over

the course of treatment, as evidenced by Kawashima. In comparing the performance of two differently modified enzymes over the course of treatment, one of ordinary skill would practice all of the claimed method steps, such that the invention as claimed would have been obvious.

Claim 19 is obvious in view of the Kawashima, Ettinger, Saito, and Francis applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, 18, and 41-46 above, and further in view of Bollin et al (US 4,678,812, of record).

The teachings of Kawashima, Ettinger, Saito, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references do not teach adding an excipient that protects asparaginase during lyophilization.

Bollin teaches that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635